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Abbreviations:

AA – African American

ADHD – Attention Deficit/Hyperactivity Disorder

aOR – adjusted odds ratio

BASC-2 – Behavioral Assessment System for Children, 2nd Edition

CCAAPS – Cincinnati Childhood Allergy and Air Pollution Study

ECAT – Elemental Carbon Attributed to Traffic

GED – General Equivalency Diploma

LUR – land use regression

NHANES – National Health and Nutrition Examination Survey

SES – Socio-Economic Status

TRAP – Traffic-Related Air Pollution

UFP – Ultrafine particle

Abstract

Background: There is increasing concern about the potential effects of traffic-related air pollution (TRAP) on the developing brain. The impact of TRAP exposure on childhood behavior is not fully understood due to limited epidemiologic studies.

Objective: To explore the association between early life exposure to TRAP using the surrogate, elemental carbon attributed to traffic (ECAT), and attention deficit/hyperactivity disorder (ADHD) symptoms at age seven.

Methods: Exposure to ECAT during infancy and behavioral scores at age seven were collected utilizing the Cincinnati Childhood Allergy and Air Pollution (CCAAPS) birth cohort. Children enrolled in CCAAPS had at least one atopic parent and a birth residence either < 400m or > 1500m from a major highway. Children were followed from infancy through age seven. ECAT exposure during the first year of life was estimated based on measurements from 27 air sampling sites and land use regression modeling. Parents completed the Behavioral Assessment System for Children 2nd Edition, at age seven. ADHD and related symptoms were assessed using the Hyperactivity, Inattention, Aggression, Conduct Problems, and Atypicality subscales.

Results: Exposure to the highest tertile of ECAT during the child's first year of life was significantly associated with hyperactivity T scores in the "at risk" range at age seven after adjustment (aOR=1.7; 95% CI: 1.0, 2.7). Stratification by maternal education revealed a stronger association in children whose mothers had higher education (aOR=2.3; 95% CI: 1.3, 4.1).

Conclusions: ECAT exposure during infancy was associated with higher hyperactivity scores in children; this association was limited to children whose mothers had more than a high school education.

Introduction

Ultrafine particles (UFP - less than 100 nm in diameter) are implicated in the pathophysiology of air pollution related disease (Zanobetti and Schwartz 2009). Research in animals and humans demonstrates that the brain may be affected by traffic related air pollution (TRAP) and in particular, UFP. Oberdorster and colleagues demonstrated translocation of inhaled ultrafine particles from the respiratory tract to extrapulmonary sites including the olfactory bulb in rats (Kreyling et al. 2002; Oberdorster et al. 2004). In an autopsy study, Calderon and colleagues reported an association between exposure to high levels of ambient air pollution and histological changes in the brain consistent with neuroinflammation (Calderon-Garciduenas et al. 2008b). Their study of otherwise normal children and young adults who died from accidents also demonstrated the presence of particulate matter in perivascular tissues of the frontal cortex. This group has also reported evidence of brain parenchymal changes on MRI and significant deficits in cognition, memory, and executive function in children exposed to high levels of ambient air pollution compared with low exposure matched controls (Calderon-Garciduenas et al. 2008a).

Epidemiologic studies have also reported associations between air pollution exposure and negative neurocognitive outcomes in school-aged children (Suglia et al. 2008; Wang et al. 2009). Exposure to black carbon (a marker of TRAP and diesel exhaust) was associated with decreased cognitive scores for verbal and nonverbal intelligence, and memory at 8–11 years of age in a longitudinal cohort population of 202 children (Suglia et al. 2008). Exposure to traffic-related air pollution (measured by NO_2 and PM_{10}) was associated with poor performance in Visual Simple Reaction Time (both preferred and non-preferred hands), Continuous Performance, Digit Symbol, Pursuit Aiming, and Sign Register assessments in a cross-sectional study of 861

children 8-9 years old (Wang et al. 2009). NO_2 exposure, a surrogate for TRAP exposure was negatively associated with cognitive development at 4 years of age in 210 boys in a European birth cohort, although the association was not statistically significant (Freire et al. 2010). Prenatal exposure to polycyclic aromatic hydrocarbons was not associated with behavioral problems at age 3 (Perera et al. 2006) but was associated with attention problems and symptoms of anxiety/depression at 6–7 years of age in a US cohort (Perera et al. 2012).

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric diagnosis in children characterized by symptoms of inattentiveness and/or hyperactivity that are present before age seven in more than one setting, and are not explained by another cause (First 2000). ADHD affects between 7 and 9.5% of children in the United States between 4 and 15 years old, or approximately 4.0 million children (Bloom and Cohen 2007; Braun et al. 2006; CDC 2010). There is a strong familial tendency for ADHD with heritability estimated to be as high as 75%; lower socioeconomic status, younger age, and male gender are associated with high prevalence of ADHD (Biederman and Faraone 2005). However, epidemiological studies suggest that both genetic and environmental factors are associated with the development of ADHD (Biederman and Faraone 2005; Braun et al. 2006). An analysis of 1999-2002 National Health and Nutrition Examination Survey (NHANES) data indicated that environmental tobacco smoke and lead were associated with ADHD (Braun et al. 2006). The impact of TRAP on childhood behavior and its potential association with ADHD is unknown, though a recent cross-sectional study reported an association between particulate matter air pollution exposure (PM_{10}) and a DSM-IV diagnosis of ADHD among 9–17 year old children (n=1819) in India (Siddique et al. 2011).

Associations between early childhood exposures to environmental chemicals and subsequent neurodevelopmental disorders have been reviewed elsewhere (Grandjean and Landrigan 2006;

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Landrigan et al. 2005). Knowledge about the deleterious effects of lead, polychlorinated biphenyls, and mercury on children's developing brains suggests that early life exposures can have significant consequences for adverse neurobehavioral outcomes later in life (Grandjean and Landrigan 2006), but the impact of TRAP on neurobehavior is less well understood. The objective of this study was to determine if exposure to TRAP during early childhood is associated with behavioral outcomes at age seven, particularly hyperactivity, attention problems, aggression, conduct problems, and atypicality, i.e., behaviors that are considered odd or strange, (Reynolds and Kamphaus 2004) which often co-exist with ADHD (Raishevich 2007; Volker et al. 2010).

Materials and Methods:

Study Design

The sample for the present analysis was drawn from participants in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS). Children enrolled in CCAAPS, a prospective birth cohort, were selected based on their residence at time of birth being either near (<400m) or far (>1500m) from a major highway or bus route (LeMasters et al. 2006). Using birth records, newborns were identified from the Cincinnati metropolitan area from 2001 to 2003. Parents who reported allergy symptoms and had a positive skin prick test to one of 15 aeroallergens were eligible to enroll their infant. Children completed annual clinical examinations at age's one through four and age seven. At each of these visits a medical history, physical exam, and skin prick test were obtained. Parents also reported the locations where their child spent at least eight hours per week during the previous year including new residences, daycare facilities or relatives'

homes. The CCAAPS study was approved by the University of Cincinnati Institutional Review Board and parents provided informed consent prior to their children enrolling in the study.

Child Behavioral Assessment

At the age seven study visit, parents completed a psychological assessment questionnaire, the Behavioral Assessment System for Children, Parent Rating Scale 2nd Edition (BASC-2) (Reynolds and Kamphaus 2004). The BASC-2 consists of 160 questions that are answered by parents as Never, Sometimes, Often, or Always. It is designed to assess a child's adaptive and problematic behaviors in both the community and home settings (Reynolds and Kamphaus 2004). The BASC-2 was validated for use on a United States school age population. After the parent completed the BASC-2, it was scored using BASC-2 scoring software (BASC-2 PRQ ASSIST™). BASC-2 scores consist of composite and subscale T scores with a mean of 50 and standard deviation of 10. All subscale scores were calculated, but hyperactivity, attention problems, aggression, conduct problems, and atypicality subscales were selected for analysis *a priori* as these symptoms often co-exist with ADHD (Raishevich 2007; Volker et al. 2010). The BASC-2 has three internal validity scores. The F ("Fake bad") index assesses whether the parent rated their child in an overly negative fashion. A high score (greater than six) on this scale suggests that the parent rated the child's behavior more severely than expected and that the results should be interpreted with caution (Reynolds and Kamphaus 2004). The Response Pattern (R) Index is a count of the number of times an individual item's response differs from the previous item's response. A high (> 125) or low (< 66) R index value suggests that parent was not attentive to content of the questions and that the results should be interpreted with caution. The Consistency Index identifies situations where the parent provided different answers to questions that are usually answered similarly. A Consistency Index score > 17 suggests that the

results should be interpreted with caution. The scoring protocol for the BASC-2 allows for no more than two missing items per each rating scale.

BASC-2 T scores were dichotomized into those in the "at risk" range or higher versus those below the "at risk" cut-off T score of 59. The "at risk" designation is used to indicate those children who have potential of developing behavioral problems on a given subscale and require careful monitoring (Reynolds and Kamphaus 2004).

Estimation of Traffic-Related Air Pollution Exposure

A complete description of the air sampling at monitoring stations and the land-use regression (LUR) methodology developed and utilized to estimate traffic-exposure for CCAAPS children has previously been described (Ryan et al. 2007; Ryan et al. 2009). Briefly, ambient air sampling was conducted on a rotating basis at 27 sampling sites in the greater Cincinnati area from 2001-2006 and the average daily concentration of elemental carbon was determined for each. The portion of sampled elemental carbon attributed to traffic (ECAT) was determined by positive matrix factorization and UNMIX receptor models (Hu et al. 2006; Sahu et al. 2011). Thus, ECAT serves as a marker of traffic-exhaust, primarily diesel exhaust (Sahu 2011). The final land-use regression model relating ECAT measured at the sampling sites to land-use and traffic variables had an r^2 of 0.73 with elevation, truck traffic within 400 m, and length of bus routes within 100 m as significant independent variables (Ryan et al. 2007; Ryan et al. 2008). A time-weighted average daily exposure to ECAT was estimated for each CCAAPS participant during their first year of life based upon parental report of locations where the child spent at least 8 hours per week, on average. The average hours per day at each of these addresses was weighted by the proportion of time spent at that location during the first year of life (Ryan et al. 2008).

For this study, we used the average daily ECAT exposure over the first year of life as the primary exposure.

Covariates

Environmental tobacco smoke (ETS) exposure during pregnancy was estimated by parental report of the number of cigarettes smoked by the mother during each trimester of the pregnancy and averaged to estimate prenatal ETS exposure. Postnatal ETS exposure during the first year of life was also obtained from questionnaire and dichotomized into exposed and non-exposed based on parental report of any cigarettes smoked in the home (Biagini Myers et al. 2012). The age of the home was used as a surrogate for lead exposure and was dichotomized based on the year the home was built (< 1950 or ≥ 1950). Cotinine measurements were obtained for at least one hair sample collected during a study visit from year one through year four. If more than one measure were available, the earliest obtained sample was used.

At the baseline visit, demographic information was collected. Maternal and paternal education were captured by five categories (did not finish high school, high school or GED, some college or trade school [up to 3 years], college [4 years or more], and graduate school) and dichotomized at completion of high school/GED or less, or some college/trade school and higher). Household income and insurance status (Medicaid) was obtained by caregiver report. Income was dichotomized at $30,000/year and Medicaid status was dichotomized (yes/no). Race/ethnicity was defined as either African American or non-African American based on parental report. Mothers reported their duration of breastfeeding at the age one clinical examination, and it was dichotomized as either > 5 months or $<= 5$ months. Breastfeeding for > 20 weeks was negatively associated with ADHD symptoms and positively associated with executive functioning at age 4

in a birth cohort of 500 children (Julvez et al. 2007a). Daycare attendance (yes/no) during the first year of life was determined by parental report of their child spending time at a babysitter, daycare, or a relative's home.

Statistical Analysis

The association between ECAT exposure and behavior problems was estimated using linear regression for continuous BASC-2 subscale scores and logistic regression for dichotomized BASC-2 subscale scores defining children "at risk." Due to the skewed distribution of ECAT exposure and the relationship between the highest tertile of ECAT exposure and recurrent night cough previously reported in this cohort (Sucharew et al. 2010), ECAT exposure was dichotomized at the highest tertile versus the lower two tertiles. An exploratory analysis was also performed with ECAT and BASC-2 scores as continuous variables.

Potential model covariates were identified based on previous work within the CCAAPS cohort linking environmental exposures with outcomes, and on established risk factors for childhood behavioral disorders, including gender, race/ethnicity, maternal and paternal education, household income, Medicaid status, duration of breastfeeding, pre- and postnatal ETS exposure, hair cotinine, age of home, and daycare attendance (Biederman and Faraone 2005; Braun et al. 2006; Julvez et al. 2007a; Julvez et al. 2007b). Factors that predicted BASC-2 hyperactivity subscale score in the "at-risk" range with $p < 0.1$ based on Chi-square tests and bivariate logistic regression were entered into multivariable models for each outcome. Co-linearity among the potential covariates was also assessed using Chi-square, Pearson correlation, ANOVA or Kruskal-Wallis, as appropriate. To avoid colinearity among several covariates that could serve as markers for socio-economic status, only maternal education was chosen to represent socio-

economic status in the multivariable models. To evaluate the potential differential impact of this variable on hyperactivity scores, additional analyses were performed. An interaction term (maternal education x ECAT) was entered into the model, and further explored by an analysis stratified by maternal education.

Statistical analysis was carried out using Epi Info 3.5.1 (CDC 2008, http://www.cdc.gov/epiinfo) and JMP 9 (SAS Institute 2010).

Results

Of the 762 children initially enrolled in the study, 617 (81%) completed the age seven clinical examination, and of these, 599 of participants (97%) completed the BASC-2. Observations were excluded from analyses if the F-Index score was less than 0, indicating a large number of missing items on the BASC-2 (n=5) , an F-Index score greater than six (n=3), a consistency score greater than 17 (n=4), or an R-index score suggesting parental inattention to the questionnaire (n=9). In addition, 2 children with missing data from the year one visit were excluded, leaving 576 children. Of these, 36 children (6%) changed residential locations between birth and the 1 year visit, and 377 children (65%) moved between the 1 year visit and the year 7 visit.

Compared to children excluded from the present analysis (n=186), those included were more likely to have mothers with more than a high school education or GED and an annual household income ≥ $30,000, and were less likely to have prenatal cigarette exposure (Table 1). The percentages of African-American children and children with homes built before 1950 were lower

but not significantly different from the excluded children. The average estimated ECAT exposure was the same in both groups.

Of the 576 children, 55% were male and 20.3% were African American. Maternal education was at the level of high school/general equivalency diploma (GED) or less for 21.3%. Eleven percent reported tobacco use during pregnancy whereas 21.6% reported tobacco exposure during the first year of life. The mean ± one standard deviation (1SD) age when the BASC-2 was administered was 6.9 ± 0.3 years. Mean T scores (± SD) for selected subscales were: Hyperactivity, 50.8 ± 10.3; Aggression, 50.3 ± 9.6; Conduct Problems, 50.8 ± 10.6; Atypicality, 49.4 ± 9.5; and Attention Problems, 50.9 ± 10.2.   Our sample T score means and standard deviation were comparable to the expected T score means (50) and standard deviation (10) based on the BASC-2 validation studies (Reynolds and Kamphaus 2004). The "at-risk" range for each BASC-2 subscale is defined as scores at or above 1 standard deviation from the mean. The percentage of children in the "at risk" range for this study is as follows: Hyperactivity 18.4%, Attention Problems 19.3%, Aggression 15.7%, Conduct Problems 14.1%, and Atypicality 14.3%.   The percentage of children with either a Hyperactivity T score or Attention T score in the clinical range for ADHD (> 69) was 9.2%.

The mean ECAT exposure estimate was $0.4 ± 0.1$ µg/m^3 (median = 0.35 µg/m^3, 33rd percentile = 0.32 µg/m^3, 66th percentile = 0.40 µg/m^3). African American race/ethnicity, having a home built <1950, maternal education ≤ high school/GED, family income <$30,000, breast feeding < 5 months, and hair cotinine were positively associated with ECAT (all p<0.001). Age of the child's home and hair cotinine were not considered for the final model because they were not significant predictors of the hyperactivity BASC-2 subscale score in the "at risk" range. Of the 451 available hair cotinine samples, 18.4% were below the limit of detection (0.02 ng/mg). For

those samples below the limit of detection, imputed values were entered into the model (Hornung and Reed 1990). In addition, we did not adjust for race/ethnicity because it was not a significant predictor of risk for a hyperactivity T score in the "at risk" range. For parsimony only maternal education was chosen to represent socio-economic status (SES) as it was significantly associated with income and Medicaid status. Maternal education was also significantly associated with duration of breastfeeding as well as an at risk range T score for hyperactivity.

Unadjusted linear regression models of BASC-2 T scores in association with ECAT as a continuous variable indicated positive association with all subscale T scores except aggression, though the association was statistically significant for atypicality only (Table 2). Scores indicating that children were at risk were significantly associated with high vs. low ECAT exposure ($\geq$0.40 vs. < 0.40 $\mu g/m^3$) for Hyperactivity, Conduct Problems, and Atypicality based on unadjusted logistic models (all p<0.01) (Table 2). After adjusting for gender, cigarette exposure during the first year of life, and maternal education, high ECAT remained significantly associated with an "at risk" score for hyperactivity only (aOR 1.7; 95% CI: 1.04, 2.73). An ECAT x maternal education interaction term was added to this model but it was not statistically significant (p=0.07).

Stratification by maternal education modified the relationship between ECAT exposure and hyperactivity. Higher ECAT exposure was associated with a significant increase in hyperactivity only among those children whose mothers had greater than a high school education (Table 3).

Discussion

To our knowledge, this is the largest prospective cohort with the longest follow-up investigating early life exposure to TRAP and neurobehavioral outcomes at school age. We observed an association between ECAT exposure and BASC-2 hyperactivity scores that appeared to be limited to children whose mothers had higher education.

Several biological mechanisms could explain the association between hyperactive behaviors and exposure to TRAP. In an autopsy study comparing children and adults who lived in a cities with either high (n=35) or low (n=12) ambient air pollution (based on $PM_{2.5}$), those in the highly exposed city (Mexico City) experienced significantly increased levels of inflammatory mediators and vasoconstrictors (Calderon-Garciduenas et al. 2008b). Neuroinflammatory changes were observed in the highly exposed group as evidenced by upregulation of cyclooxygenase-2 and interleukin-1 beta in the frontal cortex (Calderon-Garciduenas et al. 2008b). Using electron microscopy, these investigators also noted the presence of UFP within erythrocytes within the capillaries of the frontal cortex in one subject (Calderon-Garciduenas et al. 2008b). In a rat model, there is evidence of translocation of ^{13}C nanoparticles (in the UFP size range of 36 nm diameter) through the olfactory nerves (Oberdorster et al. 2004) and this is one hypothesized route into the brain. Dysfunction of frontal-cortical circuits is associated with ADHD (Biederman and Faraone 2005). Diesel exhaust particles were selectively toxic to dopaminergic neurons in a rat tissue culture system (Block et al. 2004). Although the exact biological mechanism for ADHD has not been identified, there is evidence implicating the dopaminergic system in its pathophysiology (Biederman and Faraone 2005; Froehlich et al. 2007; Kahn et al. 2003; Swanson et al. 2007).

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The association between high versus low ECAT and hyperactivity scores was limited to children whose mothers had more than a high school education. An analysis of The Multimodal Treatment Study of Children with ADHD (MTA) demonstrated a positive association between early diagnosis of ADHD and later poor school achievement (Langberg et al. 2011). One possible explanation for our finding is that lower school achievement in mothers is associated with maternal ADHD and this predisposition to ADHD symptoms is a stronger predictor of hyperactivity in their children than is ECAT exposure. In addition, mothers with higher education may expect higher achievement and this expectation may increase the parental report of behavioral concerns.

Other studies have demonstrated associations between markers of air pollution and neurobehavior in children. A positive association between residential proximity to freeways and autism has been reported in a study of 304 autism cases and 259 typically developing controls (Volk et al. 2011). In our study, we found an association between a marker of high TRAP exposure and atypical behaviors; the tendency to behave in ways that are immature, age-inappropriate or considered odd and often associated with hyperactivity (Reynolds and Kamphaus, 2004). This association remained positive but was attenuated and non-significant after adjusting for covariates. In a cohort of children from Menorca, Spain NOx exposure from indoor cooking was associated with inattention behaviors but not hyperactivity (Morales et al. 2009). We found the opposite; no association between ECAT exposure and inattention, but a positive association between ECAT and hyperactivity. There are important differences in the constituents of indoor and outdoor air pollution, with indoor NOx contribution coming mostly from indoor cooking and ECAT coming from traffic (Levy et al. 2010). A limitation of our study

is that we do not have detailed data on indoor air pollutants, nor did we model NOx in the outdoor air.

There are several other study limitations.   One limitation is that the population was selected on the basis of being at high risk for atopy, and therefore our findings may not be generalizable. However, the percentage of children with BASC-2 scores that would meet clinical criteria for ADHD was close to national estimates for ADHD prevalence. The percentage of children with either hyperactivity or inattention scores in the clinical range (9.2%) suggests that our study population is similar to the prevalence of ADHD in the general population (9.5%) (CDC 2010). In addition, associations with components of TRAP other than ECAT, including PAHs, VOCs, and gaseous pollutants, were not assessed.

In our study, childhood exposure to TRAP was estimated by applying an LUR model to locations where caregivers reported living and spending time to estimate average daily exposure to ECAT. This LUR model was developed using average daily concentrations of ECAT sampled at 27 sites in the greater Cincinnati airshed from 2001-2006.(Hu et al. 2006; Ryan et al. 2007; Sahu et al. 2011) The strength of the LUR approach is its ability to characterize exposure to pollutants with high spatial variability. A limitation to our approach, however, is that temporal variability in exposure estimates is dependent upon changes in residential or other locations. Thus, we are not able to distinguish the impact of prenatal from early childhood exposures as 94% of families remained in the same residential location from birth to age one.

Another potential limitation of the study is the lack of data regarding the behavioral health history of the CCAAPS families, including maternal hyperactivity. Childhood lead exposure is associated with ADHD (Braun et al. 2006; Froehlich et al. 2009) but blood lead levels were not

measured among the children in this study. As a surrogate, we examined the age of the home, as the majority of lead poisoning is children is caused by exposure to deteriorating paint in older buildings. However, we did not adjust for age of the home because it was not a significant predictor of hyperactivity T scores. Also, it is likely that ECAT is associated with higher traffic noise, therefore confounding by noise may bias associations with ECAT.

Among the strengths of this study is that it is a longitudinal birth cohort and that the exposure to ECAT is well characterized. The BASC-2 is a carefully validated instrument that provides scores that are applicable to a clinical setting. Finally, the population of the greater Cincinnati metropolitan area tends to be stable, and 79% of the original population completed the BASC-2. Children who completed the study did not differ in their estimated exposure to ECAT during the first year of life from those who did not complete the study, but their mothers were significantly more likely to have higher education levels.

Conclusions

Although the prevalence of ADHD in children is increasing (CDC 2010) , there is little known about potential environmental contributions to its development. Compared with children exposed to ECAT <0.40 $\mu g/m^3$ during their first year of life, children with high ECAT exposure were 70% more likely to have a high hyperactivity score after adjustment for potential confounders, with a slightly stronger association among children whose mothers had more than a high school education. Examination of age at exposure as well as gene environment interactions might also inform understanding of the pathophysiology of traffic exposure and behavior. Given that 35.2 million people in the U.S. live in counties in non-attainment of their $PM_{2.5}$ levels (EPA 2009), approximately 11% of the U.S. population lives within 100m of a four-lane highway (Brugge et

al. 2007), and 40% of children attend school within 400m of a major highway (Appatova et al. 2008), the observed association between TRAP and hyperactivity may have far-reaching implications for public health.

References

Appatova AS, Ryan PH, LeMasters GK, Grinshpun SA. 2008. Proximal exposure of public schools and students to major roadways: a nationwide US survey. Journal of Environmental Planning & Management 51(5):631-646.

Biagini Myers JM, Khurana Hershey GK, Deka R, Burkle JW, Levin LS, Bernstein DI, et al. 2012. Asking the right questions to ascertain early childhood secondhand smoke exposures. J Pediatr 160(6):1050-1051.

Biederman J, Faraone SV. 2005. Attention-deficit hyperactivity disorder. Lancet 366(9481):237-248.

Block ML, Wu X, Pei Z, Li G, Wang T, Qin L, et al. 2004. Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 18(13):1618-1620.

Bloom B, Cohen RA. 2007. Summary health statistics for U.S. children: National Health Interview Survey, 2006. Vital and health statistics Series 10, Data from the National Health Survey (234)(234):1-79.

Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. 2006. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. Environ Health Perspect 114(12):1904-1909.

Brugge D, Durant JL, Rioux C. 2007. Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. Environ Health 6:23.

Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, et al. 2008a. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn 68(2):117-127.

Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, et al. 2008b. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol 36(2):289-310.

CDC. 2010. Increasing prevalence of parent-reported attention-deficit/hyperactivity disorder among children --- United States, 2003 and 2007. MMWR Morb Mortal Wkly Rep 59(44):1439-1443.

EPA. 2009. Air Quality Trends | AirTrends | Air & Radiation | EPA. Available: http://www.epa.gov/airtrends/aqtrends.html#comparison [accessed 08/21/2011.

First MB. 2000. Diagnostic and Statistical Manual - Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.

Freire C, Ramos R, Puertas R, Lopez-Espinosa MJ, Julvez J, Aguilera I, et al. 2010. Association of traffic-related air pollution with cognitive development in children. J Epidemiol Community Health 64(3):223-228.

Froehlich TE, Lanphear BP, Auinger P, Hornung R, Epstein JN, Braun J, et al. 2009. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics 124(6):e1054-1063.

Froehlich TE, Lanphear BP, Dietrich KN, Cory-Slechta DA, Wang N, Kahn RS. 2007. Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. Biol Psychiatry 62(3):243-249.

Grandjean P, Landrigan PJ. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368(9553):2167-2178.

Hornung RW, Reed LD. 1990. Estimation of average concentration in the presence of nondetectable values. Applied Occupational and Environmental Hygiene 5(1):46-51.

Hu S, McDonald R, Martuzevicius D, Biswas P, Grinshpun SA, Kelley A, et al. 2006. UNMIX modeling of ambient PM(2.5) near an interstate highway in Cincinnati, OH, USA. Atmos Environ 40(S2):378-395.

Julvez J, Ribas-Fito N, Forns M, Garcia-Esteban R, Torrent M, Sunyer J. 2007a. Attention behaviour and hyperactivity at age 4 and duration of breast-feeding. Acta Paediatr Suppl 96(6):842-847.

Julvez J, Ribas-Fito N, Torrent M, Forns M, Garcia-Esteban R, Sunyer J. 2007b. Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. Int J Epidemiol 36(4):825-832.

Kahn RS, Khoury J, Nichols WC, Lanphear BP. 2003. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. J Pediatr 143(1):104-110.

Kreyling WG, Semmler M, Erbe F, Mayer P, Takenaka S, Schulz H, et al. 2002. Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J Toxicol Environ Health 65(20):1513-1530.

Landrigan PJ, Sonawane B, Butler RN, Trasande L, Callan R, Droller D. 2005. Early environmental origins of neurodegenerative disease in later life. Environ Health Perspect 113(9):1230-1233.

Langberg JM, Molina BS, Arnold LE, Epstein JN, Altaye M, Hinshaw SP, et al. 2011. Patterns and predictors of adolescent academic achievement and performance in a sample of children with attention-deficit/hyperactivity disorder. Journal of clinical child and adolescent psychology : the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53 40(4):519-531.

LeMasters GK, Wilson K, Levin L, Biagini J, Ryan P, Lockey JE, et al. 2006. High prevalence of aeroallergen sensitization among infants of atopic parents. J Pediatr 149(4):505-511.

Levy JI, Clougherty JE, Baxter LK, Houseman EA, Paciorek CJ. 2010. Evaluating heterogeneity in indoor and outdoor air pollution using land-use regression and constrained factor analysis. Research report (Health Effects Institute)(152):5-80; discussion 81-91.

Morales E, Julvez J, Torrent M, de Cid R, Guxens M, Bustamante M, et al. 2009. Association of early-life exposure to household gas appliances and indoor nitrogen dioxide with cognition and attention behavior in preschoolers. Am J Epidemiol 169(11):1327-1336.

Oberdorster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, et al. 2004. Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol 16(6-7):437-445.

Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, Diaz D, et al. 2012. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6-7 years. Environ Health Perspect 120(6):921-926.

Raishevich NJ, Peter. 2007. Attention-deficit/Hyperactivity Disorder. In: Nelson Textbook of Pediatrics, Part 18th (Kliegman RMB, Richard E.; Jenson, Hal B.; Stanton, Bonita F., ed). Philadelphia, PA:Saunders Elsevier.

Reynolds CR, Kamphaus RW. 2004. BASC-2 Behavioral Assessment System for Children. Circle Pines, MN: AGS Publishing.

Ryan PH, Lemasters GK, Biswas P, Levin L, Hu S, Lindsey M, et al. 2007. A comparison of proximity and land use regression traffic exposure models and wheezing in infants. Environ Health Perspect 115(2):278-284.

Ryan PH, Lemasters GK, Levin L, Burkle J, Biswas P, Hu S, et al. 2008. A land-use regression model for estimating microenvironmental diesel exposure given multiple addresses from birth through childhood. Sci Total Environ 404(1):139-147.

Sahu M, Hu S, Ryan PH, Le Masters G, Grinshpun SA, Chow JC, et al. 2011. Chemical compositions and source identification of PM(2.5) aerosols for estimation of a diesel source surrogate. Sci Total Environ 409(13):2642-2651.

Siddique S, Banerjee M, Ray MR, Lahiri T. 2011. Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. Eur J Pediatr 170(7):923-929.

Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. 2008. Association of black carbon with cognition among children in a prospective birth cohort study. Am J Epidemiol 167(3):280-286.

Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, et al. 2007. Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. Neuropsychol Rev 17(1):39-59.

Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. 2011. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect 119(6):873-877.

Volker MA, Lopata C, Smerbeck AM, Knoll VA, Thomeer ML, Toomey JA, et al. 2010. BASC-2 PRS profiles for students with high-functioning autism spectrum disorders. J Autism Dev Disord 40(2):188-199.

Wang S, Zhang J, Zeng X, Zeng Y, Chen S. 2009. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. Environ Health Perspect 117(10):1612-1618.

Zanobetti A, Schwartz J. 2009. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environ Health Perspect 117(6):898-903.

Table 1: Demographic characteristics and environmental exposures for children either included or excluded from study analysis

	Included n=576			Excluded n=186		
	No.	**%**	**Mean±SD**	**No.**	**%**	**Mean±SD**
Demographic Characteristics						
Age when BASC-2 administered	576		6.9±0.3			NA
African American	117	20.3		49	26.3	
Male	317	55.0		98	52.7	
Mother's education level (HS/GED or less)*	119	21.3		66	35.9	
Family income <$30K*	131	23.5		71	38.6	
Environmental Exposures						
ECAT Exposure Year 1	576		0.4±0.1	186		0.4±0.1
Hair cotinine (Year 1-4)*	451		0.2±0.3	123		0.2±0.4
Prenatal cigarette exposure*	57	10.5		33	18.2	
Cigarette exposure Year 1	110	21.6		47	29.2	
Home built before 1950	134	26.9		38	36.2	
Past Medical History						
Any positive SPT in 2 or more years	260	45.1				
Any ADHD medications Year 7	17	3.0				
BASC-2 T scores, year 7 (continuous)						
Hyperactivity	576		50.8±10.3			
Inattention	576		50.9±10.2			
Aggression	575		50.3±9.6			
Conduct Problems	576		50.9±10.6			
Atypicality	576		49.4±9.5			
BASC-2 T scores "at-risk" range [a]						
Hyperactivity	106	18.4				
Attention Problems	111	19.3				
Aggression	90	15.7				
Conduct Problems	81	14.1				
Atypicality	82	14.3				

Abbreviations: ECAT, Elemental Carbon Attributable to Traffic; SPT, skin prick test

[a] At-risk range = T-score > 59

* $p < 0.05$ comparing children included and excluded from analysis

Table 2: Association between BASC-2 T scores and ECAT exposure during the first year of life among 576 children

BASC-2 Subscale	ECAT (μg/m³) and continuous score[a]		Total in "at risk" range	"At risk" with high ECAT exposure	ECAT (dichotomous)[b] and "at risk" score, unadjusted		ECAT (dichotomous)[b] and "at risk" score, adjusted[c]	
	β	95% CI	n	n	OR	95% CI	OR	95% CI
Hyperactivity	5.1	(-1.2, 11.4)	106	48	1.9	(1.2, 2.9)[**]	1.7	(1.0, 2.7)[*]
Attention problems	4.3	(-1.8, 10.4)	111	44	1.4	(0.9, 2.2)	1.1	(0.6, 1.7)
Aggression[d]	0.0	(-5.7, 5.7)	90	37	1.5	(0.9, 2.4)	1.2	(0.7, 2.0)
Conduct problems	6.1	(-0.2, 12.4)	81	39	2.1	(1.3, 3.3)[**]	1.5	(0.9, 2.6)
Atypicality	6.8	(1.1, 12.5)[*]	82	39	2.0	(1.3, 3.2)[**]	1.5	(0.9, 2.6)

[a] Association between BASC-2 subscale score (continuous) and a 1- μg/m³ increase in ECAT, unadjusted linear regression model.

[b] Association between "at risk" BACS-2 subscale score and high vs. low ECAT ($\geq$ 40 μg/m³ vs. <0.40 μg/m³), logistic regression model

[c] Adjusted for gender, report of environmental tobacco smoke (ETS) exposure in the first year of life, and maternal education. In the adjusted analysis, those missing maternal education (n=18) and ETS exposure (n=66) were excluded (total n = 504).

[d] due to missing data for one child with lower ECAT exposure, n=575 for the continuous analysis and unadjusted OR, n=503 for the adjusted OR

[*] $p<0.05$

[**] $p<0.01$

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Table 3: Odds ratio (OR) with 95% confidence interval (CI) from logistic regression for associations between at risk scores for ADHD-related BASC-2 subscales[a] and high versus low ECAT exposure during the first year of life[b], stratified by maternal education high school or less vs. greater than high school

| | | **Lower maternal education n=119** | | | | | | **Higher Maternal Education n=439** | | | | |
| | | Unadjusted | | Adjusted[d] | | | | Unadjusted | | Adjusted[d] | | |
BASC-2 Scale	n[c]	OR	95% CI	OR	95% CI	p	n[c]	OR	95% CI	OR	95% CI	p
Hyperactivity	18	0.9	(0.4, 1.9)	0.9	(0.4,2.2)	0.83	29	2.4	(1.4,4.1)[*]	2.3	(1.3,4.1)[*]	0.003
Attention Problems	20	0.8	(0.4,1.7)	0.8	(0.3,1.8)	0.97	21	1.4	(0.8,2.4)	1.3	(0.7,2.4)	0.40
Aggression	13	0.7	(0.3,1.7)	0.6	(0.2,1.7)	0.34	24	1.9	(1.1,3.4)[*]	1.5	(0.8,2.8)	0.16
Conduct Problems	17	1.3	(0.6,2.9)	1.1	(0.4,2.8)	0.88	21	2.2	(1.2,3.9)[*]	1.7	(0.9,3.2)	0.14
Atypicality	18	1.4	(0.6,3.2)	1.6	(0.6,4.1)	0.31	17	1.7	(0.9,3.2)	1.4	(0.7,2.8)	0.30

[a] BASC-2 T score > 59

[b] ECAT $\geq$ 40 µg/m^3 vs. <0.40 µg/m^3

[c] Number with at risk T score and high ECAT

[d] Adjusted for gender, and age one cigarette exposure.

[*] $p < 0.05$